Clinical review

Evidence based case report

Twenty year cough in a non-smoker

Paul Glasziou

Editorial by Godlee

University of Queensland Medical School, Queensland 4006, Australia

Paul Glasziou, *reader in clinical epidemiology*

P.Glasziou@spmed.uq.edu.au

BMJ 1998;316:1660–1

Mrs V was a 66 year old woman who said she had had a non-productive cough almost daily for 20 years. This had been treated unsuccessfully in the past with antibiotics, but she was not taking any medication currently. Mrs V had good exercise tolerance, although she had an occasional wheeze at night. She was a non-smoker and had never lived with smokers. Her chest was normal on examination. Her peak expiratory flow rate was 500 (with a predicted value of 380), and her spirometry result was good and showed minimal (<5%) response to β agonist. Nevertheless, because asthma is an intermittent but common cause of cough, and because Mrs V had complained of nocturnal wheeze, I decided to try her on a β agonist aerosol (an alternative would have been an inhaled steroid, but the response to treatment would have taken longer). Meanwhile, I resolved to track down the evidence about other possible causes of Mrs V's cough.

Searching for evidence

The first step was to formulate an answerable clinical question[1]—one of aetiology, differential diagnosis, diagnostic test accuracy, prognosis, treatment, or prevention. Here the initial clinical question was one of differential diagnosis: what are the possible causes, and frequency, of a chronic cough?

My favourite ambulatory care text, *Primary Care Medicine*,[2] listed 20 possible causes of chronic cough. These included environmental irritants such as smoking; lower respiratory tract problems such as lung cancer and asthma; upper respiratory tract problems such as chronic rhinitis or sinusitis; extrinsic compressive lesions such as aortic aneurysm; and miscellaneous causes such as psychogenic cough and reflux oesophagitis. Progressive conditions such as cancer or bronchiectasis were unlikely as Mrs V's condition had not changed over the 20 year course.

The further information I needed was a differential diagnosis that included the frequency of possible causes. The chapter in *Primary Care Medicine* did not give the relative frequency for all diagnoses but did discuss two studies. Was this the best evidence on which to base my management? Preferably these studies would have investigated a large, consecutive, and representative series of patients with sufficient follow up to make any misdiagnosis apparent.

Unfortunately, most relevant studies are not coded as such in Medline. The search requires two components—firstly, chronic cough or synonyms, and secondly, a "methodological filter"—to confine it to appropriate studies of differential diagnosis. A Medline search using "chronic *near* cough" (the special term *near* means that the "chronic" and "cough" need to be close together but allows for terms such as "chronic non-productive cough") yielded 343 references in just the past five years. This was too many, so the search needed to be confined to articles that were potentially most relevant. I felt that a reasonable methodological filter might be to try to restrict references to those with an appropriate sample—that is, a random or consecutive set of cases, plus an adequate yardstick test or tests, and an appropriate follow up (to catch missed or mistaken diagnoses). Putting this together, I tried the following search: "chronic *near* cough," "investigat* *or* diagnos* *or* cause*," and "consecutive *or* follow up".

This search produced the four studies described in the table,[3–6] including the two that had been discussed in *Primary Care Medicine*. These studies had used somewhat different diagnostic yardsticks, but, following Irwin,[4] all required a response to specific treatment as a criterion for diagnosis. Given this need to establish response, the follow up in most studies was quite acceptable. Of particular interest was the structured approach to empirical treatment described by Pratter (I now keep a copy of this useful algorithm in my clinic desk).[6]

Evidence into practice

The β agonist treatment for one week had no effect on Mrs V's cough, but she did admit to acid regurgitation (this symptom has a sensitivity of 45% and specificity of 88% for endoscopic oesophagitis).[7] She also had experienced some minor nasal symptoms, but these were not currently a problem. Given that acid reflux was the next most likely cause of the cough, I needed to choose between empirical treatment or oesophageal pH monitoring. Since access to pH monitoring is difficult and fairly costly I decided to treat her reflux with simple measures. I discussed the options with her. She was not worried that the reflux indicated serious disease but was irritated by the cough. Mrs V did not relish the travel and time involved in investigations; she preferred the idea of trying simple empirical treatment first.

Studies found by a Medline search on causes of chronic cough

	Poe[3]	Irwin[4]	Mello[5]	Pratter[6]
Setting	Community	Referral	Consecutive, referral	Consecutive, referral
Yardstick	Retrospective review, including response to treatment	Chest *x* ray, other*, plus response to treatment	Questionnaire, chest *x* ray, other*, plus response to treatment	Questionnaire, respiratory function tests, other*, plus response to treatment
Eligible/followed up	134/139	49/?	88/98	45/61
Asthma (%)	21	24	14	29
Postnasal drip (%)	19	41	38	56
Acid reflux (%)	4	21	40	11
Post infectious (%)	9	—	—	—
Chronic bronchitis, bronciectasis (%)	4	5	4	—
Other (%)	—	—	8	4
Undiagnosed (%)	14		2	

*Other investigations were done as indicated by history, examination, and other test results.

Outcome

There are many treatments for oesophageal reflux. One published report already in my files described a randomised factorial trial of the individual and combined effects of ranitidine and raising the bed head in patients with severe peptic oesophagitis.[8] This showed that combined treatment had approximately equal and additive effects. I could find no direct evidence from randomised trials that acid reduction alone was sufficient. Therefore, as a simple first measure, I asked Mrs V to raise the head of her bed 10-15 cm and take 20 ml of magnesium and aluminium hydroxide antacid at night (similar to the treatment used by Irwin). The cough settled within a few days and six months later had not recurred.

Few of my colleagues nominated oesophageal reflux as a cause of chronic cough, but most acknowledged it when reminded. What was more surprising to me and my colleagues was its frequency as a cause of chronic cough. However, the diagnosis is not simple, as many patients will not complain of reflux symptoms and oesophageal monitoring is not easily obtained. Thus, empirical treatment may be a reasonable course in cases such as Mrs V's, where there is no urgency to resolve the problem and the selected treatment is safe. The ideal might have been to do an "n-of-1" trial—that is, to have Mrs V randomised to be on and off treatment for several periods. This would have established the cause more clearly … but a suitable placebo for raising the head of the bed escapes me.

My thanks to Professor David Sackett and an anonymous referee for helpful comments.

Funding: None.

Conflict of interest: None.

1 Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM*. London: Churchill Livingstone, 1997.
2 Goroll AH, May LA, Mulley AG. *Primary care medicine. Office evaluation and management of the adult patient*. Philadelphia: Lippincott, 1995.
3 Poe RH, Harder RV, Israel RH, Kallay MC. Chronic persistent cough: experience in diagnosis and outcome using an anatomic diagnostic protocol. *Chest* 1989;95:723-8.
4 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981;123:413-7.
5 Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996;156:997-1003.
6 Pratter MR, Bartter T, Akers S, DuBois J. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;119:977-83.
7 Jenkinson LR, North C, Watson A. Symptoms and endoscopic findings—can they predict abnormal nocturnal acid gastrooesophageal reflex? *Ann R Coll Surg Engl* 1989;71:117-9.
8 Harvey RF, Hadley N, Gill RR, Beats BC, Gordon PC, Long DE. Effects of sleeping with the bed-head raised and of ranitidine in patients with severe peptic oesophagitis. *Lancet* 1987;2:1200-3.

(Accepted 9 October 1997)

Lesson of the week

Scurvy in patients with cancer

Olivier Fain, Emmanuel Mathieu, Michel Thomas

Weakness, bleeding, purpura, and gingivitis in patients with cancer may be due to scurvy

Scurvy is caused by a deficiency of vitamin C (ascorbic acid) and still occurs in developed countries. Those most at risk of scurvy are elderly people, men who live alone, people who are dependent on alcohol, people with fadish diets,[1] mentally ill patients, and those undergoing peritoneal dialysis and haemodialysis.[2] Scurvy is not usually reported in patients with cancer but its frequency is probably underestimated.

We describe six cases of scurvy in patients with cancer.

Case reports

From January 1993 to September 1996 we observed six cases of scurvy in 3723 patients with non-cancerous conditions and six cases in 219 patients with cancer. Tables 1 and 2 give details of the six cases in the patients with cancer. All of the patients were men. Two of them (cases 2 and 4) lived alone and three (cases 1, 2, and 4) drank heavily. All of them had a low serum vitamin C concentration as measured by liquid chromatography, and their condition improved with supplemental vitamin C.

Case 1—A 58 year old man with diabetes mellitus was admitted with a month's history of weakness, weight loss, and anorexia. Clinical examination showed spontaneous ecchymosis, intramuscular haemorrhage on the back, and hepatosplenomegaly. Gingivitis was present. His haemoglobin concentration was 140.5 g/l,

continued over

Table 1 Details of six patients with cancer who developed scurvy

Case No	Neoplastic disease	Associated factors	Clinical manifestations of scurvy
1	Polycythaemia vera, myelofibrosis	Diabetes mellitus, high alcohol intake	Intramuscular haemorrhage
2	Metastatic adenocarcinoma of colon	High alcohol intake, smoking	Haemorrhagic gingivitis
3	Chronic myelomonocytic leukaemia, mastocytosis		Intramuscular haemorrhage
4	Metastatic squamous cell carcinoma of lung	High alcohol intake, smoking	Haemorrhagic gingivitis
5	Chronic myelomonocytic leukaemia		Haemorrhagic gingivitis, purpura
6	Metastatic prostatic carcinoma	Smoking	Purpura

Table 2 Laboratory results of six patients with cancer who developed scurvy

Case No	Serum vitamin C (μmol/l) (range 45-90)	Serum cholesterol (mmol/l) (range 4.4-6.4)	Serum albumin (g/l) (range 40-60)	Selected laboratory results
1	6	2.2	36	
2	<6	4.6	26	Microcytic anaemia, low serum iron concentration 4 μmol/l (range 12-32)
3	<6	3.3	45	Bleeding time 18 minutes
4	<6	5	25	Macrocytic anaemia
5	<6	3.7	25	Macrocytic anaemia, folate <2 nmol/l (range 4-22)
6	<6	3.6	30	Macrocytic anaemia

Department of Internal Medicine, Jean Verdier Hospital, 93140 Bondy, France
Olivier Fain, *senior registrar*
Emmanuel Mathieu, *consultant*
Michel Thomas, *senior consultant*
Correspondence to: Dr Fain olivier.fain@jvr.ap-hop-paris.fr

packed cell volume 50.3%, leucocyte concentration 3.6×10^9/l, platelet concentration 697×10^9/l, and serum cholesterol concentration 2.2 mmol/l (normal range 4.4-6.4). Folate and serum iron concentrations were normal. No coagulation disorders were found. Polycythaemia vera was diagnosed from a total red cell mass of 53 ml/kg (normal range 26-36), with myelofibrosis evident on bone marrow biopsy. Serum vitamin C concentration was 6 μmol/l (normal range 45-90) (table 2). He received 2 g of vitamin C daily, and the haematoma and gingivitis resolved in 1 week.

Case 2—A 50 year old man had adenocarcinoma of the colon and hepatic and lung metastases. After a second course of fluorouracil and folinic acid chemotherapy he developed haemorrhagic gingivitis. Fluorouracil toxicity was suspected, but because he had persistent gingivitis and had lost 20 kg in weight in 3 months his serum vitamin C concentration was assayed (<6 μmol/l). His haemoglobin concentration was 83 g/l, mean corpuscular volume 64 fl, serum iron concentration 4 μmol/l (normal range 12-32), and albumin concentration 26 g/l. Serum cholesterol concentration was normal (table 2). No coagulation disorders were found. He received 2 g of vitamin C daily, and the gingivitis resolved within a few days.

Comment

Scurvy should be considered in patients with cancer because of the high incidence of malnutrition caused by the chemotherapy, cachexia caused by the disease, and other factors that might lead to an unbalanced dietary intake—for example, exclusive parenteral nutrition, depression, impaired taste, dysphagia, and abdominal pain. Radiotherapy can also cause mucosal atrophy of the small intestine, leading to malabsorption. Increased energy expenditure and inefficient energy utilisation are often noted in patients with cancer,[3] and their requirements for vitamin C may also be increased as in smokers[4] and people with diabetes.[5] The symptoms of scurvy occur rapidly after 1-3 months of vitamin C deficiency when the body's reserve is <300 mg (normal 1500 mg).

Weakness, anorexia, and depression are common in scurvy but also in patients with cancer. Clinicians should suspect vitamin C deficiency when a patient has haemorrhagic features without a clear explanation and swollen, bleeding gums.[1 2]

Scurvy is diagnosed from clinical findings and a low serum vitamin C concentration. Serum vitamin C concentration, however, reflects mainly recent dietary intake. Measuring the concentration of ascorbate in leucocytes is a useful assay because it more closely reflects the body's vitamin C stores. This test, however, is not routinely available. Treatment of scurvy consists of 1 g of vitamin C daily for 2 weeks. Clinical manifestations resolve within 2 weeks. Usually a daily dose of 60-100 mg of vitamin C prevents scurvy (one 100 g orange contains 50 mg of vitamin C).

In patients with cancer, bleeding and gingivitis are not necessarily secondary to the disease or chemotherapy but may be due to scurvy. Deterioration and death may occur if this diagnosis is missed.

1 Reuler JB, Broudy VC, Cooney TG. Adult scurvy. *JAMA* 1984;253:805-7.
2 Ghorbani AJ, Eichler C. Scurvy. *J Am Acad Dermatol* 1994;30:881-3.
3 Daly JM, Hoffman K, Lieberman M, Leon P, Redmond HP, Shou J, et al. Nutritional support in the cancer patient. *J Parenter Enteral Nutr* 1990;14:244-8S.
4 Schectman G. Estimating ascorbic acid requirements for cigarette smokers. *Ann NY Acad Sci* 1993;686:335-45.
5 Cunningham JJ, Ellis SL, McVeigh KL, Levine RE, Calles-Escandon J. Reduced mononuclear leukocyte ascorbic acid content in adults with insulin-dependent diabetes mellitus consuming adequate dietary vitamin C. *Metabolism* 1991;40:146-9.

(Accepted 11 September 1997)

Fifty years ago

The new NHS: Safeguards secured

The Special Representative Meeting called to consider the results of the April plebiscite and the recommendations of Council last Friday brought to an end a debate which has lasted nearly six years by passing the Council's recommendation advising the medical profession to co-operate in the National Health Service. The meeting also had before it a letter from the Ministry of Health outlining the proposed content of the Amending Bill and referring to other matters recently discussed. This letter and an account of the meeting are recorded in this week's Supplement. By deciding to co-operate the Representative Body brought BMA policy into line with responsible public opinion, and has confirmed its reputation for sane judgment in the world of medical politics. (*Editorial*, 5 June 1948, p 1086. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)